Old Herborn University Seminar Monograph 36: The microbiome and cancer.
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A MICROBIOTA-MODULATED CHECKPOINT DIRECTS IMMUNOSUPPRESSIVE INTESTINAL T CELLS INTO CANCERS

Introduction

The topic of the presentation of *Dr. Marine Fidelle* (Gustave Roussy Cancer Campus, Villejuif Cedex, France) was "*A microbiota-modulated checkpoint directs immunosuppressive intestinal T cells into cancers*". She started with pointing at an European consortium (*PREVALUNG EU, N°101095604*) that is aiming at finding biomarkers based on multi-omics and associated with cancer and microbiome for cancer prevention and early diagnosis.

Chemotherapy and the recent advent of immunotherapies have improved the results of the treatment of cancer, and the role of the microbiome is increasingly recognised in oncology. Immune checkpoint inhibitors (ICB) is a type of immunotherapy that reinvigorate the immune system to eliminate cancer cells, but for many patients, the treatment is ineffective from the start (primary resistance) or becomes ineffective over time (acquired resistance). These patients have a significant unmet clinical need for other treatments or combinations to overcome this resistance. Overcoming resistance to immunotherapy remains a challenge for patients and society. During the last decade, several studies have shown that a "favourable" gut microbiome composition can have an impact on the outcome of anticancer treatment (*Viaud* et al., 2013; *Vetizou* et al., 2015; *Daillère* et al., 2016; *Routy* et al., 2018; *Roberti* et al., 2020; *Derosa* et al., 2020; *Fluckiger* et al., 2020; *Dart*, 2020; *Hanahan*, 2022).

Cancer-associated gut microbiota deviation (dysbiosis)

Fifty years ago, some papers already showed that malignant diseases could be associated with a change in the intestinal barrier (*Deller* et al., 1967; *Gilat* et al., 1972). Recently, Laurence Zitvogel's team discovered that the intestine can sense cancer development. It is linked to the balance between the sympathetic and parasympathetic signalling in the intestine and involved enteroendocrine cells. Pharmacologic blockade of beta-adrenergic receptors by betablockers limited the growth of extra-intestinal tumours, in this way preventing cancer-induced ileopathy characterized by an alteration of the crypt and villus ratio (*Yonekura* et al., 2022). This change of the gut epithelial barrier fitness and permeability culminated in a long-lasting dysbiosis (*Yonekura* et al. 2022). Indeed, three to seven days after a tumour is subcutaneously implanted in mice, the gut microbiota is affected with a change of composition, resulting in a dominance of Gram-positive *Enterocloster* species (formerly, *Clostridium* species). This is also observed in patients as shown in figure 1. This figure shows, through metagenomic analysis, the deviation of the gut microbiota composition in patients with cancer across several cancer types in comparison to healthy volunteers (HV).

The gut onco-microbiota signatures (GOMS)

Dr. Fidelle discussed a rationale for an impact of the gut microbiome in cancer immuno-modulation. Primary resistance to immune checkpoint inhibitors (ICBs) is a phenomenon in which cancer treatments become ineffective, notably due to immune evasion mechanisms.

Resident gut bacteria can affect patient responses to cancer immunotherapy. Thomas and colleagues have shown that the composition of the gut microbiota can predict clinical outcomes in patients treated with ICB and have defined the gut onco-microbiota

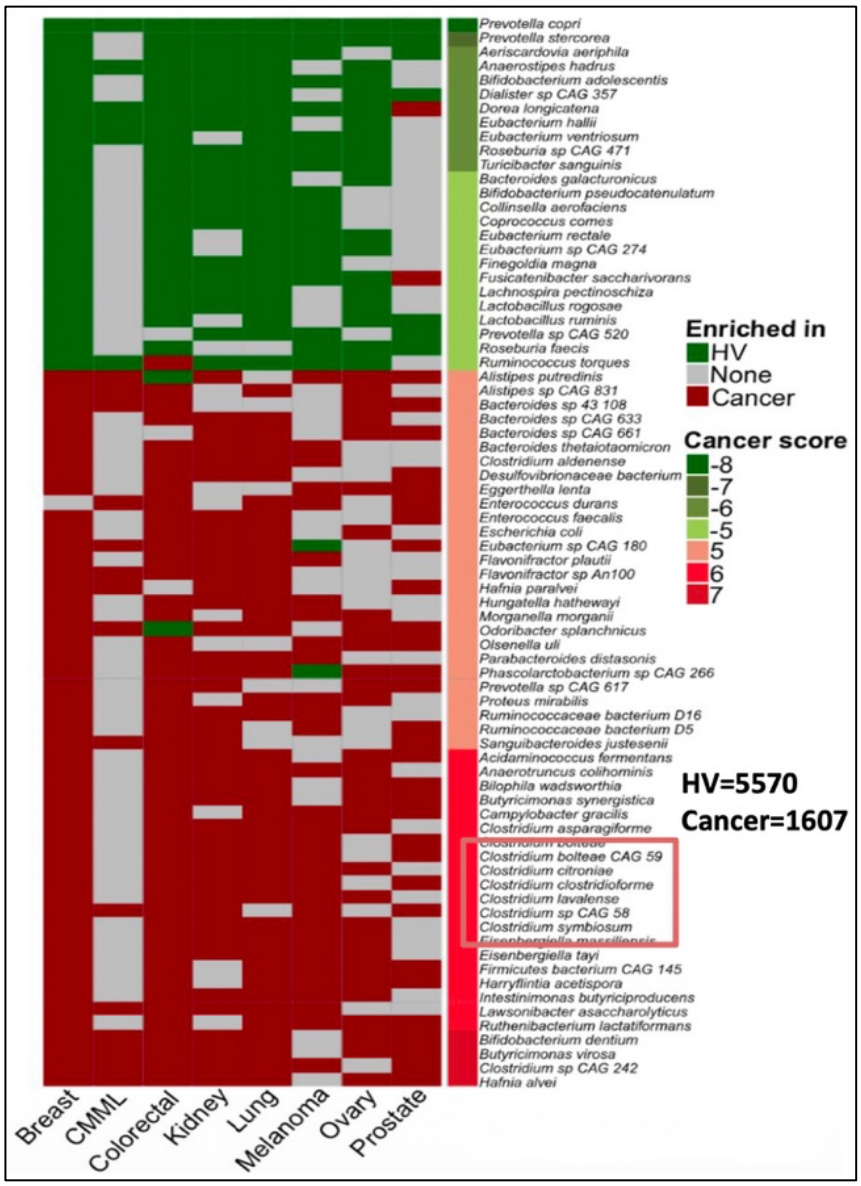

Figure 1: Heatmap showing the dominance of *Clostridium* spp. In five out of eight cancer categories. (Figure from *Yonekura*, 2022)

signatures (GOMS) (*Thomas* et al., 2023). They found that non-responding patients with lung or kidney cancer had low levels of the bacterium *Akkermansia muciniphila*. Likewise, two other studies in melanoma patients receiving ICB found a greater abundance of other "favourable" bacteria in the guts of responding patients. Non-responders had an imbalance in gut flora composition, which correlated with impaired immune cell activity. Finally, metanalysis found common patterns between cancer-driven dysbiosis and non-response to ICB, such as an overrepresentation of bacteria from *Enterocloster* spp. (*Park* et al., 2022) Thus, maintaining healthy gut flora could help

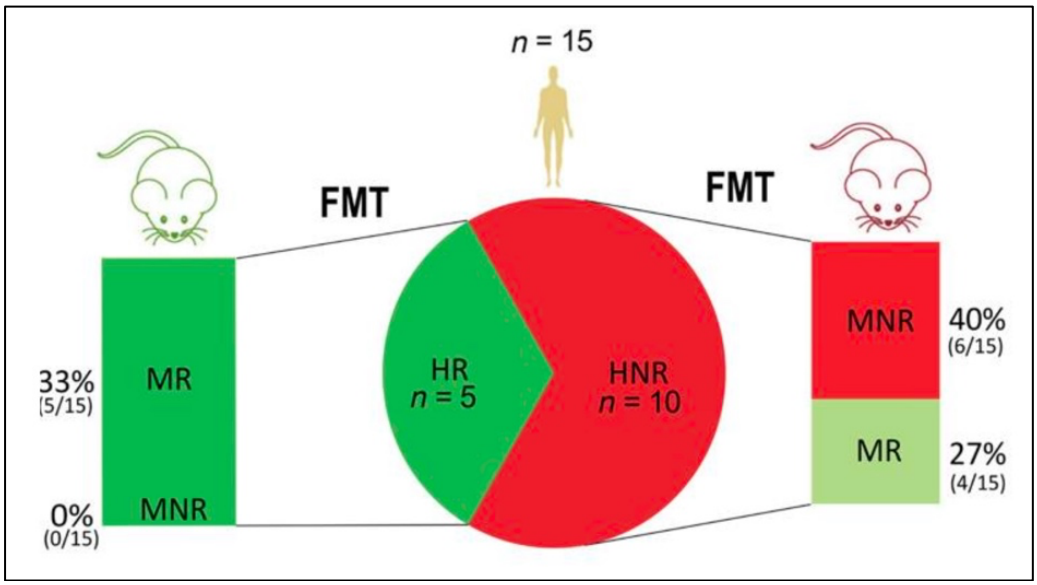

Figure 2: Proportion of the response in mice that matches the clinical response of the corresponding patient, based on the 15 FMT donors (human responders [HR] and non-responders [HNR]) and their outcomes in mice (mouse responders [MR] and non-responders [MNR]).(Figure from *Derosa* et al., 2020).

patients combat cancer (*Routy* et al., 2018; *Matson* et al., 2018; *Gopalakrishnan* et al., 2018; *Park* et al., 2022).

Dr. Fidelle explained their use of an avatar mice model to demonstrate the causal relationship between patient gut microbiota and ICB efficacy. Avatar mice refer to an experimental method employed to transplant the gut microbiota of a donor into mice. Here, stool samples were collected from patients before they started ICB and transplanted into the intestines of mice via faecal microbiota transplantation (FMT). Then they inoculated the tumour subcutaneously and treated the mice with ICB. The effectiveness of the treatment in mice actually corresponded to the patients' response to their immunotherapy, meaning that the composition of the patient's gut microbiota at the initiation of the treatment has an impact on the response to immunotherapy (*Routy* et al., 2018). (Figure 2).

They also have shown that antibiotics known to alter the gut microbiota composition ("dysbiosis") were associated with poor response to ICB as PD-1/PD-L1 blockade in patients with lung or kidney cancers. A retrospective meta-analysis done by Dr. Derosa and colleagues on multiple clinical studies comprising about 12 000 patients, confirmed that antibiotics has a negative impact on the success of immunotherapy with reduced overall survival (*Derosa* et al., 2020). Antibiotics facilitated the dominance of distinct species such as *Enterocloster spp.*, which were also preferentially over-represented in stools from patients with a cancer compared to healthy volunteers or non-responder patients (*Park* et al., 2022; *Fidelle* et al. 2023).

Development of tools to diagnose gut microbiota dysbiosis in patients

Given the importance of gut microbiota composition on the response to immune checkpoint blockers (ICB), it is essential to be able to diagnose dysbiosis in patients who will receive this treatment. This requires the development of diagnostic tools that are easy to use routinely.

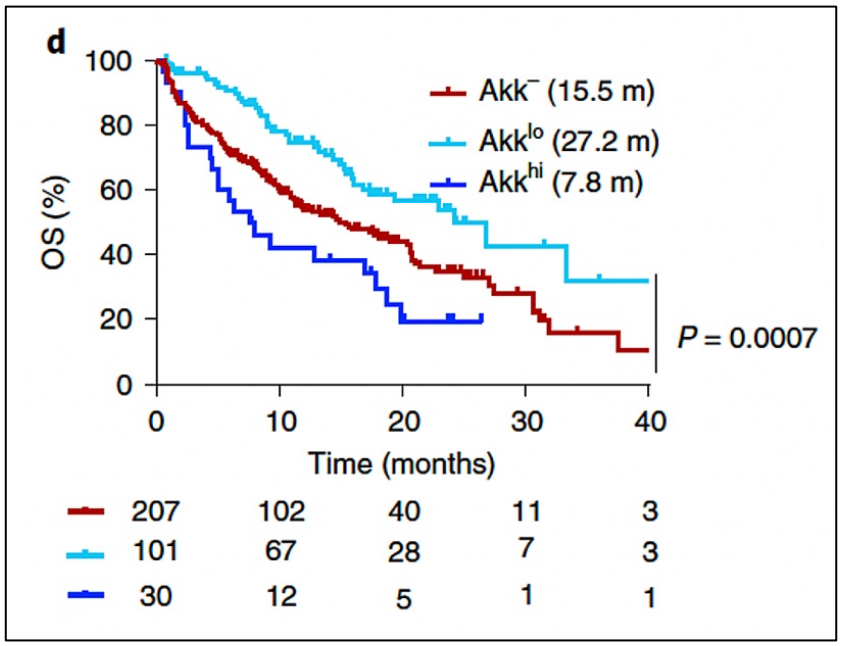

Figure 3: Overall survival (percentage) of non-small cell lung cancer patients according to *Akkermansia muciniphila* (Akk) relative abundance, segregated in 3 groups (Akk^{-}, Akk^{low} and Akk^{high}). (Figure from *Derosa* et al., 2022)

Routy, and colleagues have shown that patients having the bacterium *Akkermansia muciniphila* in their stools benefited from ICB in lung and renal cell cancers (*Routy* et al., 2018; *Derosa* et al 2022). Furthermore, oral supplementation of the bacterium *Akkermansia muciniphila*, in antibiotic-treated mice colonized with flora from non-responder patients restored the response to immunotherapy (*Routy* et al., 2018). Surprisingly, patients with high levels of *Akkermansia muciniphila* (Akk^{hi}) showed a lower overall survival in comparison to the ones with lower levels (Akk^{lo}), as depicted in Figure 3.

To diagnose dysbiosis, Derosa and colleagues developed a score based on the composition of patients' stools (*Derosa* et al., 2024). This was done by the construction of species-level co-abundance networks, based on metagenomics (MG) sequencing of 245 NSCLC patient faeces. The network analysis clustered bacteria into species-interacting groups (SIGs) correlating with overall survival. Thirty-seven and forty-five MG species (MGSs) were associated with poor (SIG1) or favourable (SIG2) clinical outcomes, respectively, in patients treated with ICB. Quantification of SIG1 and SIG2 bacteria yields a continuous score (from 0 to 1) where the extremes, <0.5 or >0.8, are associated with an unfavourable or favourable composition, respectively, for clinical response. However, a "grey zone" remains and when combining the quantification of *Akkermansia muciniphila*, this procedure allowed a person-based calculation of a topological score (TOPOSCORE). This score was validated in an additional 254 NSCLC patients and in 216 genito-urinary cancer patients. Finally, this TOPOSCORE was translated into a 21-bacterial probe set-based quantitative real-time PCR (qPCR) scoring that was validated in a prospective cohort of NSCLC patients as well as in colorectal and melanoma patients. This approach could represent a dynamic diagnosis

tool for intestinal dysbiosis to guide personalized microbiota-centred interventions (*Derosa* et al., 2024).

As previously reported, antibiotics can be harmful when taken close to the initiation of immunotherapy (*Routy* et al., 2018; *Derosa* et al., 2020). Fidelle and colleagues investigated whether bacteria that recolonise after discontinuation of antibiotic treatment may affect the treatment response. She has shown that *Enterocloster* species, that recolonized the guts of mice or patients treated with antibiotics, down-regulated the expression of the mucosal addressin cell adhesion molecule 1 (MAdCAM-1), the ligand for integrin α4β7 that helps to retain an enterotropic subset of T cells within the gut. In mice, the downregulation of MAdCAM-1 expression on intestinal high endothelial venules leads to a recirculation of immunosuppressive IL-17 secreting Treg cells (Tr17 cells) to tumours and tumour-draining lymph nodes, where they compromise immune checkpoint blockade therapy (*Fidelle* et al., 2023).

In cancer patients undergoing immunotherapy, low levels of serum-soluble MAdCAM-1 (sMAdCAM-1) correlated with intestinal dysbiosis, defined by a decrease of bacterial diversity and an overabundance of *Enterocloster* spp. or *Veillonella* spp. in their gut microbiota and poor clinical outcomes for renal, bladder, and lung tumours (*Fidelle* et al., 2023). Therefore, sMAdCAM-1 may be an easy-to-measure biomarker in the blood for dysbiosis and response to immunotherapy in patients.

These two scores pave the way for the rapid routine diagnosis of intestinal dysbiosis, and open the door to a microbiota-centred intervention (MCI), such as the use of faecal microbiota transplantation (FMT), pre- and pro-biotics and also the administration of *Akkermansia* spp. to correct the dysbiosis.

Microbiota-centred interventions (MCI)

Given the accumulating evidence on the importance of the gut microbiota in the efficacy of ICB, MCI could be a way to overcome primary resistance to ICB in patients. Therefore, two faecal microbiota transplantation (FMT) studies were conducted in melanoma patients with primary resistance to ICB.

Dr. Baruch and colleagues performed a phase 1 clinical trial to assess the safety and feasibility of FMT and reinduction of anti-PD-1 immunotherapy in 10 patients with anti-PD-1-refractory metastatic melanoma. They observed clinical responses in a third of patients, including two partial responses and one complete response, indicating a role of the gut microbiota in cancer treatment (*Baruch* et al., 2021).

Similar results were obtained by Dr. Davar and colleagues in a clinical trial evaluating the safety and efficacy of responder-derived FMT together with anti-PD-1 in patients with PD-1-refractory melanoma. This combination was well tolerated, provided clinical benefit in 6 of 15 patients, and induced rapid and durable microbiota modification (*Davar* et al., 2021). They concluded that FMT and anti-PD-1 changed the gut microbiome and reprogrammed the tumour microenvironment to overcome resistance to anti-PD-1 in a subset of PD-1 advanced melanoma.

Conclusion

The study of the microbiota in oncology has made it possible to determine its impact on the antitumor immune system and the response to treatments. Mechanisms such as the loss of MAdCAM-1 expression, or the understanding of its composition (GOMS), have led to the development of dysbiosis scores (Toposcore, sMAdCAM-1 assay) that can be easily used routinely by oncologists. These advances pave the way for

the use of microbiota-centred interventions (MCI), such as FMT, to correct dysbiosis in patients and enhance their chances of responding to immunotherapies.

This paper was reviewed by Dr. Marine Fidelle before publishing.

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